Kidney International, Vol. 49 (1996), pp. 1534–1538

Contributions of clinical medicine to renal physiology

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The strong influence of clinical medicine on the development of renal physiology in the 20th century is a natural consequence of the striking disorders imposed by disease on the volume and composition of the fluids of the body. Clinicians well grounded in physiology were able to seize unusual opportunities provided by sick patients to elucidate principles of homeostatic control applicable to health as well as to disease. Three examples of such contributions, primarily originating at the bedside, are discussed: the role of potassium in metabolic alkalosis, the function of the parathyroid glands as exemplified by the syndrome of hyperparathyroidism, and the discovery of a humoral factor, distinct from parathyroid hormone, that may regulate phosphate excretion by the kidneys.

More than any other branch of biology, the flowering of renal physiology in the 20th century, to which Homer Smith contributed so much, has been a collaboration between clinical medicine and physiology. Some examples that come easily to mind are listed in Table 1, and the first three are described in this short account.

The control of the volume and composition of body fluids is the subject in which the powerful influence of clinicians upon the shape of renal physiology is most evident, when the development of medical science in Homer Smith's lifetime is examined. It is natural that this should be so, because of the striking disorders imposed by disease, which impelled clinicians in the first half of this century, armed with new advances in chemical techniques and concepts, to seek answers to their questions. Perhaps the best example of the seminal role of the clinician in the development of renal physiology is that of Daniel C. Darrow (Fig. 1).

Dr. Darrow, a Professor of Pediatrics at Yale Medical School when I was a student there in the mid-1940's, was born in Kansas and looked, acted and dressed like a working Kansas farmer. He had a practical man's mild contempt for fancy statistics. If you needed statistics to tell you whether your results were significant or not, he would say, the results probably weren't important. Instead, he applied the most sophisticated conceptual analysis to data collected laboriously over days and weeks, consisting of chemical measurements of the intake and excreta of sick babies. In his work and that of his contemporaries the balance technique, easier to apply to human patients than to animals, was raised to a high level as a tool of renal physiology.

He came to New Haven from Kansas via St. Louis, Missouri in the 1930's, to study disorders in body chemistry produced by children's diseases, of which the most important and the most prevalent was diarrhea. Sixty years ago the state of knowledge of sodium and potassium was summed up by John P. Peters in the first edition of his classic, *Quantitative Clinical Chemistry Interpretations*. At that time these metallic ions were called "bases" because their hydroxides were produced when an electrical current was passed through a solution of their salts.

"Potassium is the predominant base in human muscle and blood cells; sodium in the extracellular fluids. Concerning the origin of this inequality we have no explanation. We merely know that it exists. . . . We are brought to the conclusion that the cells are not ordinarily permeable to either of these cations; but concerning the property of the cell membranes or any other restraining force which prevents their free diffusion we have not the slightest idea" [1].

The pathogenesis of metabolic gastric alkalosis, it was believed, had been adequately described in 1927 by James Gamble, the young Harvard pediatrician. Gamble showed that in rabbits in which the stomach outlet was surgically obstructed and in children with congenital pyloric stenosis the disturbance was due to the loss of hydrochloric acid in gastric secretions. The resulting changes in body composition were considered to be largely confined to the extracellular fluids. According to these concepts, the only deficits susceptible to fluid therapy were losses of water, sodium and chloride. Gamble considered that the bicarbonate concentration was high owing to loss of chloride, and when recovery occurred, that chloride was displaced by bicarbonate. Similarly, diarrheal dehydration was produced by losses of water, sodium and chloride in the stools. Emphasis was placed on the losses of sodium and chloride because the losses of potassium which were known to occur were regarded as an accompaniment of starvation and tissue breakdown. The therapeutically important losses were regarded as extracellular water, sodium and chloride.

In the 1930's Darrow began to challenge the unspoken assumption that intracellular composition was inviolate with some experiments in rats and rabbits in which muscle composition was analyzed using the assumption that tissue chloride was mainly extracellular in location. He found, indeed, that intracellular concentrations of sodium and potassium could vary widely, particularly during experimental potassium depletion. Then, in 1941, he saw an unusual patient [2].

Raymond Accabo, a male infant, was born on October 26, 1941 weighing 5 pounds. From the day of birth he had diarrhea. The consequent dehydration was treated by subcutaneous injections of salt and water, and he improved, but the diarrhea continued. At the age of nine months he was admitted to Dr. Darrow's care at the New Haven Hospital, where he was again treated for dehydration and recovery seemed satisfactory the next day. On the following day Darrow visited Boston and heard James Gamble discuss the data accumulated over a period of a year on his case of congenital alkalosis with diarrhea [3]. On Darrow's return to New Haven, his patient had again become dehydrated owing to

Table 1. Some contributions of clinical medicine to renal physiology

- Potassium depletion in diarrhea—Daniel Darrow
- Parathyroids, calcium and bone—Joseph Aub, Walter Bauer, Fuller Albright
- Tumorigenic osteomalacia: a clue to the regulation of renal phosphate excretion—Rajiv Kumar
- Aldosterone, hypertension and potassium depletion—Jerome Conn
- Sulfanilamide as a diuretic—William B. Schwartz
- Renal transplantation—John P. Merrill, Joseph Murray
- "Effective blood volume" as a regulator of salt and water excretion—John P. Peters
- Nephrogenic diabetes insipidus: Water babies and aquaporins—Crawford, Ausiello, Agre, Bichet, Harmon, Strange
- Liddle's syndrome: Constitutive activation of the sodium channel—Grant Liddle, David Warnock

Table 2. Balance studies during increase and decrease of alkalosis

Period	Serum HCO_3	Conc. Cl	mEq/liter Na		Balance mEq Na	K	K[a]	Cl
1A	35	61	138	Total	−16	−62		−32
1B	47	55	124	Cell	+50	−60	−69	
3A	45	51	129	Total	+97	+77		+86
3B	35	69	138	Cell	−40	+71	+54	

Period 1 was milk mixture only for three days. Dehydration and metabolic alkalosis increased during this period.

Period 3 was a milk mixture with added KCl. Saline hypodermoclyses given daily. Recovering from dehydration and alkalosis.

[a] K balance corrected for N balance (1 g N for e mEq K) [4].

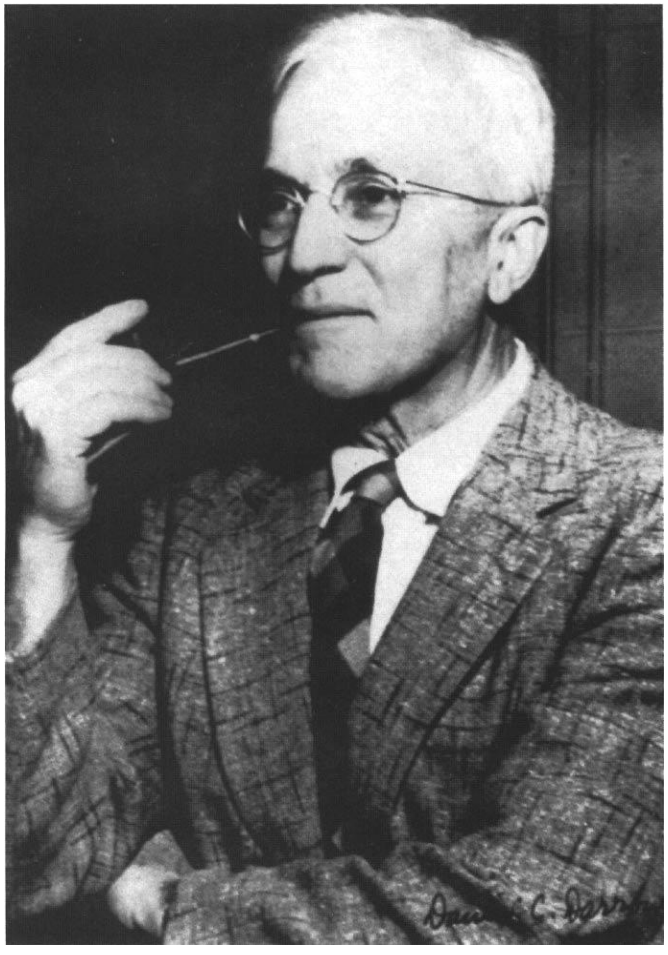

Fig. 1. *Dr. Daniel Darrow at Yale.*

diarrhea and the serum analyses showed extremely high bicarbonate and extremely low chloride. There had been no vomiting. It was obvious to him that his patient was like Dr. Gamble's and he could study Raymond with the benefit of Gamble's findings.

The characteristic features of these two patients were marked metabolic alkalosis and the passage of voluminous watery stools since birth. The systemic alkalosis distinguished them from the ordinary diarrhea of infants, usually attended by acidosis because of stool losses of bicarbonate. In these two babies, the stools contained more chloride than sodium and considerable potassium. Serum bicarbonate was always high and chloride always low. Serum potassium was often low. The urine was always essentially free of chloride. Despite the continuous watery stools, protein, fat and carbohydrate were well absorbed. The alkalosis could not be corrected with sodium chloride, and ammonium chloride produced only a temporary fall in bicarbonate. A key feature in Darrow's case was that potassium was somewhat more successful in restoring serum bicarbonate and chloride concentrations, even though in retrospect it was clear that he did not give large enough doses of potassium salts.

Over the next two years Raymond Accabo was hospitalized almost continuously in the New Haven Hospital under the care of Dr. Darrow. Without the benefit of a modern clinical research center, but with meticulous attention to detail on the part of his doctors and nurses, and with daily visits from the Kansas pediatrician, balance studies producing results like those illustrated in Table 2 were accumulated. This Table shows the essential difference between feeding with a milk mixture alone (period 1) and with the same milk mixture to which potassium chloride had been added (period 3). Diarrhea continued at essentially the same rate during both periods. Without potassium, a negative balance of potassium ensued, largely derived from the cells, and alkalosis worsened, with an increase in serum bicarbonate and a fall in serum chloride. When potassium was added, as in period 3, potassium balance became positive, potassium entered cells, serum bicarbonate fell, serum chloride rose, and, notably, serum sodium increased toward normal. Darrow later wrote that *"it was this patient with congenital alkalosis with diarrhea who made me certain that metabolic alkalosis is accompanied by loss of muscle potassium and retention of sodium in the cells. It was this patient who made me confident that the administration of potassium to infants with diarrhea would be beneficial if the deficits of potassium were as great as I expected"* [4].

Darrow's discovery of the importance of potassium was largely responsible for the dramatic drop in mortality from infantile diarrhea from about 25% to less than 5% in the course of a few years [5]. It played a major role as well in stimulating physiological investigations into the way in which potassium enters and leaves cells, exchanging for sodium and protons, through active pumping, by passive movement through membrane channels, and via the complicated mechanism of co-transport. The genetic message and complex structure of these membrane proteins are only now, 50 years later, being elucidated by physiologists, many of them workers from time to time at the Mount Desert Island Biological

Laboratory, who utilize the advanced techniques of electrophysiology, isotopic tracers and molecular biology that Darrow never knew.

There is a personal postscript to this story. In 1970 in New Haven, Howard Levitin and I studied Raymond Accabo again. Although he had required 18 hospital admissions until age 16 and had difficulty as an infant gaining weight, he had grown to a height of 6′-2″ and weighed about 300 pounds. The watery diarrhea had continued and he had never had a formed stool. He had developed gout at the age of 22 but was now symptom-free while taking Allopurinol to inhibit uric acid production. He had developed fasting hyperglycemia and glycosuria one year before at the age of 28, but these abnormalities had been almost completely corrected by potassium repletion and weight reduction. He was actively employed full-time. Although he had proteinuria and was excreting between 2 and 6 grams of protein in 24 hours, other tests of renal function were normal, as was his blood pressure. Balance studies with analyses of stool and urine confirmed the persistence of a chloride-losing diarrhea [6]. Mr. Accabo agreed to undergo further studies at the National Institutes of Health by John Fordtran, Phillip Gorden, and Fred Bieberdorf. He was intubated with a triple lumen tube, and it was concluded from studies of absorption by the ileal mucosa that there was a defect in the normal process by which chloride absorbed from the lumen was exchanged for bicarbonate [7]. We postulated that Raymond's gargantuan appetite had permitted an intake of potassium sufficient to balance the losses in stool and in urine consequent to his alkalosis, and thereby permit him to grow normally and to lead a reasonably normal life.

The next example of a signal contribution of a patient and his doctors to renal physiology is the story of Captain Charles E. Martell. Hyperparathyroidism was unknown in this country until the diagnosis was first made by Dr. Eugene F. DuBois in 1926, in the case of Captain Martell, a mariner who had become disabled by demineralization of the skeleton over many years. Eventually, a parathyroid adenoma was removed from the mediastinum at his seventh operation in 1932 at the Massachusetts General Hospital.

Charles Martell was born in 1896 in Somerville, Massachusetts, now part of Boston (Fig. 2) [8]. He entered the Merchant Marine, served on convoy duty throughout World War I, and was the picture of health until the age of 22, in 1918. At that time he noted the passage of milky urine containing gravel and complained of pains in his right flank. A year later fellow officers kidded him about the fact that he was growing shorter and had a pigeon breast and had to wear a larger collar because his neck was shorter and thicker than it had been [9]. He sustained several fractures after minor trauma and the jars of walking, particularly when going downstairs, caused him pains in the heels, legs and back (Fig. 3) [8]. No longer able to work, he entered Bellevue Hospital in 1926 under the care of Dr. Eugene DuBois, a prominent metabolic investigator who had established the first metabolic ward in this country under the auspices of the Cornell Medical Service. After several months of study, DuBois concluded that the softening of the bones from demineralization was due to a "hyperactivity of the parathyroid bodies." Because the metabolic ward at Bellevue was about to close for the summer, DuBois called up Joseph Aub and Walter Bauer at the Massachusetts General Hospital, and arranged to have the patient transferred to that hospital for further study. The three were close friends and members of the Interurban Clinical Club. DuBois knew that Aub had been interested in the parathyroid glands and had in fact injected patients suffering from lead poisoning with parathyroid extract in an attempt to mobilize lead deposited in the bones.

Fig. 2. *Captain Charles Martell in 1918, a few months before his first symptom (used with permission from The Journal of Urology [8]).*

In 1926 knowledge of parathyroid physiology and its relation to the kidney and the bones was still fragmentary. Unlike other anatomical landmarks, which had been well known for centuries, the glands had remained undescribed until first recognized in 1862 during the dissection of an Indian rhinoceros that had died in the London Zoo. Removal of the parathyroids from animals was demonstrated 30 years later at the turn of the century to result in

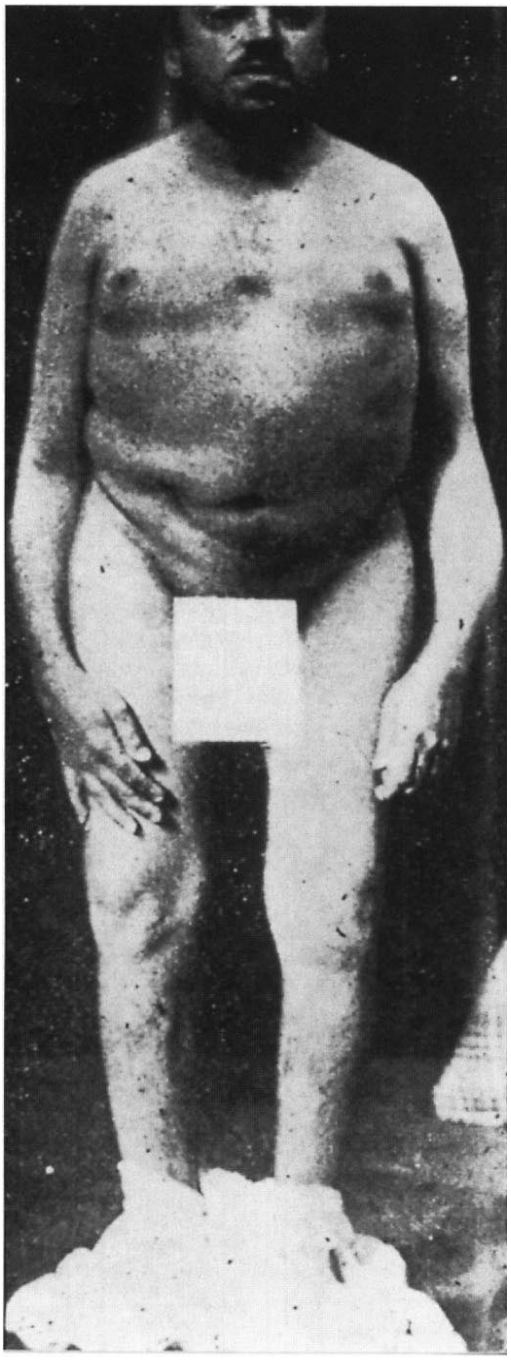

Fig. 3. *Martell at time of entry to the hospital, 1926 (used with permission from The Journal of Urology [8]).*

tetany, from which the injection of fresh parathyroid extract afforded relief. In 1909 hypoparathyroid tetany in dogs was found to be associated with a low serum calcium and in 1918 this was shown in humans as well. Only one year before Martell was hospitalized, J.P. Collip, the Toronto biochemist who had just succeeded in purifying insulin from the pancreas, produced a stable, concentrated extract of bovine parathyroid glands that prevented hypocalcemia in parathyroidectomized dogs, and when given in large amounts produced the first example of experimental hyperparathyroidism with marked hypercalcemia. In that same year of 1925 the famous Viennese surgeon Felix Mandl removed a parathyroid tumor from a patient with kidney stones and a bony disorder remarkably resembling that of Captain Charles Martell, with marked clinical improvement. At the time, however, neither DuBois, Aub, nor Bauer knew of this report [10].

At the Massachusetts General Hospital the significant chemical abnormalities measured in New York by Dr. DuBois in Captain Martell's blood were confirmed. His serum calcium was elevated at 14.8 mg% and the phosphorus was low. The fecal calcium was low and the urinary calcium high. These alterations in calcium and phosphorus metabolism were the same as those that had been observed by Dr. Aub in normal human subjects who were receiving 100 units of parathyroid extract per day. In May and again in June of 1926 the surgeons removed one and then a second parathyroid gland from Martell's neck. Both appeared normal, and Martell's symptoms continued with no change in the abnormal serum chemistries or balance studies. He was discharged on a high calcium diet because this had been able to produce a positive balance of calcium, and he felt improved, with diminished pain and weakness. By 1931, however, he was dependent on crutches and unable to lift his legs to mount stairs or enter a car. A third operation was performed in March 1932 in New York City with no tumor being discovered, and in May 1932 he returned to the Massachusetts General Hospital.

The findings were now worse than before. Martell now had many more bone cysts, clubbing of the fingers, and now calcifications of the kidney cortex with definite renal stones and marked functional impairment of the kidneys. Three further operations on the neck found no tumor. The Captain, who was often found in his room poring over an anatomy text, was now convinced that the tumor was to be sought in the chest, where abberant parathyroid glands were sometimes found, and he urged a mediastinotomy. Finally, in November 1932, after 14 years of symptoms, after approximately 18 months of study in two metabolic wards, following six previous operations, a sternum splitting procedure was carried out by Dr. Edward D. Churchill, who found a brown tumor in the mediastinum at the end of a long pedicle which took origin in the neck. The tumor was excised, the serum calcium fell rapidly, and the bones began to improve. A month later he was able to stand. Then one day one of the kidney stones became lodged in his ureter and required surgical intervention. This was followed by a series of complications, and death occurred six weeks after the removal of his tumor.

The essential features of parathyroid physiology in relation to the intestine and kidneys are to be found in the summary of the extensive studies on Captain Martell [8]. In comparison with normal subjects, the serum calcium was high and the serum phosphorus low. Despite hypercalcemia, fecal excretion of calcium was low. Urinary excretion of calcium was high on some occasions, but on others it was normal or below normal in spite of hypercalcemia, implying excessive reabsorption of calcium from the glomerular filtrate. Marked hypophosphatemia was present; in spite of this, urinary phosphorus was always high, indicative of the effect of parathyroid hormone to reduce phosphorus reabsorption by the kidneys. The careful study of this remarkable patient served as a model for subsequent studies of calcium and phosphorus metabolism, many of them carried out on the same research wards of the Massachusetts General Hospital by Fuller Albright, then in 1926 a junior staff physician who had just joined the team of Joseph Aub and Walter Bauer. The dramatic nature

of Martell's illness and its surgical treatment, and the essential facts of parathyroid physiology exemplified in the studies of his physiologically-minded doctors served for the remainder of this century to stimulate further explorations of the physiology of calcium and phosphorus in mammalian physiology.

My third example of the contribution of clinical medicine to renal physiology is taken from more recent times; in fact it is still in progress. It also concerns the intensive study of a single patient by a clinician broadly grounded in basic science and it illustrates the importance of the conjunction of a chance opportunity with a prepared mind. I think Homer Smith would have liked it.

Although, as we have just seen, it was clear as early as the 1920's that phosphate excretion was controlled by the parathyroids, it was also apparent that the renal excretion of phosphorus must be regulated by additional factors. About two-thirds of the phosphorus we eat is absorbed from the intestines and, in the steady state, excreted in the urine. This occurs through a process of glomerular filtration and subsequent tubular reabsorptions. In mammals (unlike fish), as far as we know no phosphate is secreted. Most of the reabsorption takes place in the proximal tubule through a process of sodium-linked cotransport, with a sodium/P_i cotransporter located in the apical membrane of proximal tubular cells. It would obviously be biologically advantageous for the reabsorption of phosphorus to be controlled independently of calcium metabolism, and this is what seems to take place when dietary phosphorus is manipulated. Under these circumstances urinary phosphate excretion changes greatly without obvious changes in the excretion of calcium or the secretion of parathyroid hormone. But the mechanism responsible for this fine regulation of renal reabsorption of filtered phosphate is not yet known.

In 1974 a 47-year-old woman with the rare syndrome of oncogenic osteomalacia entered the Mayo Clinic, complaining of muscular aches and weakness. She developed a spontaneous fracture of the left femur. A nontender movable mass, less than an inch in diameter, was identified in the subcutaneous tissues overlying the front lower part of the thigh. In patients like this, vascular tumors containing cells suggesting their mesenchymal origin, looking vaguely like fibroblasts and termed sclerosing hemangiomas, are associated with a generalized condition of bone resembling rickets. The serum phosphorus is very low and there is a correspondingly elevated excretion of phosphorus in the urine. Serum alkaline phosphatase is elevated, as in other cases of rickets caused by vitamin D deficiency. The serum calcium is usually normal. Removal of the tumor causes prompt correction of the syndrome, with elevation of the serum phosphorus to normal, reduction in renal phosphorus excretion, and healing of bones. In our Mayo Clinic patient, that is what happened. The subcutaneous tumor over the thigh was removed, a complete remission was obtained and the patient felt well.

In 1991, however, the tumor recurred. With it, all of the original signs and symptoms returned. The serum phosphorus fell, urinary phosphorus increased, serum alkaline phosphatase went up, and bony aches and pains returned. The patient was again studied, this time by Dr. Rajiv Kumar, a nephrologist with considerable experience in research on vitamin D and disorders of calcium and phosphorus metabolism. The diagnosis of phosphate-wasting rickets was confirmed, and it seemed likely that the kidneys were being impelled to excrete abnormal amounts of phosphorus, reducing tubular reabsorption of phosphates, because of a humoral signal elaborated by the tumor. Again the tumor was removed and again symptoms and signs regressed. Phosphate excretion returned to normal. This time, Dr. Kumar was able to culture cells from the tumor and to maintain them in culture for long periods of time. The tumor was found to elaborate a protein product that dramatically inhibited sodium phosphate cotransport in mammalian proximal tubular cells derived from the opossum kidney. Unlike parathyroid hormone, this substance did not increase cyclic AMP production and the inhibition of phosphate cotransport was not inhibited by antibodies to human parathyroid hormone [11]. It seems very likely that this substance, made in excessive amounts by these rare tumors, either is, or closely resembles, the natural regulator of phosphate absorption by mammalian renal tubules that is responsible for the maintenance of phosphorus balance by our kidneys, the guardians (as Homer Smith thought of them) of homeostasis of the sea within us.

I would like to conclude by returning to the beginning of my story and quoting from Daniel C. Darrow. Almost 40 years ago, in 1957, he wrote: *"With an eye on budgets, administrators of medical schools and hospitals connected with medical schools may be willing to let clinical research be done elsewhere. The clinical investigator may be regarded as an amphibian who is not well adapted to the environment of pure research or that of clinical medicine. . . . There is a large region that involves both the clinic and the laboratory where a rich life can be lived in a truly amphibian environment. Exploration of this area is essential to the development of real university clinical departments. If a university department in a medical school does not recognize that the study of disease is an essential function, the students are not likely to be prepared for the essential mental processes of medical practice; they will not come in contact with the advanced students of disease and will not be well prepared for objective evaluation of the advances in medical science that are sure to come"* [4].

Four decades later, on the 100th anniversary of the birth of Homer Smith, we would do well to heed that warning.

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